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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,561	08/25/2003	Michael David Bentley	034848/268660	3230

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NEKTAR THERAPEUTICS
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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	**PAPER NUMBER**
1654	
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10/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,561	BENTLEY ET AL.	
	Examiner	Art Unit	
	Thomas S. Heard	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 6-19, 23-, 24, 26, and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-19, 23-, 24, 26, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 IDSs*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/3/2007 has been entered.

The Applicants Amendments to the claims received on 8/3/2007 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 2/5/2007 are hereby withdrawn.

Claim(s) 1-3, 6-19, 23-, 24, 26, and 27 are pending. Applicants have amended claim(s) 1, 3, 6, 7-9, 11-13, 17-19, 26, and 27. Applicant's have cancelled Claims 4, 5, 20-22, and 25. Claims 1-3, 6-19, 23-, 24, 26, and 27 are hereby examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-3, 6-19, 23-, 24, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention.

In the instant case, the claims are drawn to (Claim 1) *a hydrophilic polymer-peptide conjugate consisting essentially of a peptide that is either biphalin or [D-Pen2, D-Pen5] enkephalin (DPDPE) covalently linked to one or more a water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol,);- or copolymers of ethylene glycol and propylene glycol,*

wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier, and wherein said one or more polymer chains optionally possesses an agent covalently attached thereto, wherein said agent is selected from the group consisting of a neuroactive agent, doxorubicin, an imaging agent and a diagnostic agent. The independent claim uses open language of "consisting essentially of" which, without a limiting definition is also open language. Applicants have not used the term in the specification cannot, therefore, have a limited definition of the term. Further, the wherein clause of the

(1) Level of skill and knowledge in the art:

The level of skill to practice the art of the instantly claimed invention is high with regard to conception, experimental design, synthesis, implementation of the experimentation, and data interpretation.

(2) Partial structure: (3) Physical and/or chemical properties: and (4) Functional characteristics:

Neuropeptides of bihphalin, D-Pen2 and D-Pen5 enkephalin, where in the instantly elected peptide Biphalin (Tyr-D-Ala-Gly-Phe-$NH)_2$, is a unique opioid peptide analog that contains two active enkephalin pharmacophores and is more potent than morphine.

(5) Method of making the claimed invention:

Peptide synthesis, either solution or solid phave chemistries well know to the peptide artisan.

As stated supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim neuroactive agent, an imaging agent and a diagnostic agent are a broad generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of diagnostic agent, imaging agent, or neuroactive agent. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. "MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. There are a few examples such as PEG-Dynorphin A, PEG-Endomorphin II, PEG-Doxorubicin to Endomorphin I, PEG to DPDPE, and PEG to Biphalin found in the specification on page 16-18, for example. While having written description for these PEGylated peptides and one with a specific dual conjugate (Doxorubicin) identified in the specification tables and/or examples, the specification is void of any peptides, organic molecules that qualify for the functional characteristics claimed as the biomolecules, and polymers with functional characteristics that qualify. There is insufficient description of a neuroactive agent, diagnostic agent, and imaging agent that would allow one of skill in the art to practice the invention as claimed. The description requirement of the patent statue requires a

description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-19, 21, 23, 26, and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Delgado C, Francis GE, Fisher D., "The uses and properties of PEG-linked proteins," Crit Rev Ther Drug Carrier Syst. 1992;9(3-4):249-304 and Wu D, Pardridge WM., "Neuroprotection with noninvasive neurotrophin delivery to the brain," Proc Natl Acad Sci U S A. 1999 Jan 5;96(1):254-9.

In the instant case, the claims are drawn to (Claim 1) *a hydrophilic polymer-peptide conjugate consisting essentially of a peptide that is either biphalin or [D-Pen2,*

D-Pen5] enkephalin (DPDPE) covalently linked to one or more a water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol,);- or copolymers of ethylene glycol and propylene glycol, wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier, and wherein said one or more polymer chains optionally possesses an agent covalently attached thereto, wherein said agent is selected from the group consisting of a neuroactive agent, doxorubicin, an imaging agent and a diagnostic agent. Further limitations of the claims are drawn to branched PEG chains and Chains of various lengths.

Delgado et al teaches the beneficial uses and properties of PEG-linked proteins and peptides. Delgado et al teaches a wide range of benefits of PEGylating a protein which are increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility, among other properties of the PEG-protein conjugates. Unrelated PEG-proteins are shown to have these beneficial properties demonstrating the broad acceptance of the conjugated PEG to the proteins, and that the PEG is determining the property. Delgado et al further teaches mono-pegylation, bi- and multiple-pegylation, N-terminal PEGylation and PEGylation in ranges from 700 to 70,000 MW readable upon n ranging from 10 to 2000 for $-CH_2CH_2O-(CH_2CH_2O)_n-CH_2CH_2-$ in claim 27. See entire Review Article. Delgado et al does not teach the pegylation of the neuropeptide BDNF or biphalin.

Wu et al teaches a neuropeptide (BDNF) that has been PEGylated (2000 MW) and further chemically modified to include a biotin/OX26Mab composition (diagnostic agent by the Applicant's specification) on the terminus of the PEG for transport across the blood brain barrier (BBB). Thus, the neuropeptide (BDNF) had the benefits of PEGylation taught by Delgado et al with the added capacity to transport across the BBB. Wu et al states that "there are more than 30 known neurotropic factors and there molecules may prove to be powerful neuropharmaceuticals should they be enabled to undergo transport through the BBB with optimized plasma pharmacokinetic properties. The results of the present investigation indicate that if the neurotrophic factor undergoes a defined molecular reformulation both to enable BBB transport [biotin/OX26Mab] and the addition of PEG [Pegylation] to optimize plasma pharmacokinetics then these molecules may have therapeutic effects in the brain after peripheral administration," see full article.

It would have been obvious at the time of the instantly claimed invention to substitute PEGylate biphalin for BDNF taught by Wu et al for the benefits of increased plasma half-life, reduced renal clearance, reduced cellular clearance, reduced proteolysis, reduced immunoclearance, reduced immunogenicity and antigenicity, and increased solubility among other as taught by Delgado et al. One would have been motivated to do so given that the benefits of PEGylation are not protein specific as also demonstrated by Delgado et al. One would have had a reasonable expectation of success given that many unrelated proteins have been PEGylated and shown to have these benefits and that PEGylation is a well-known and common modification in the

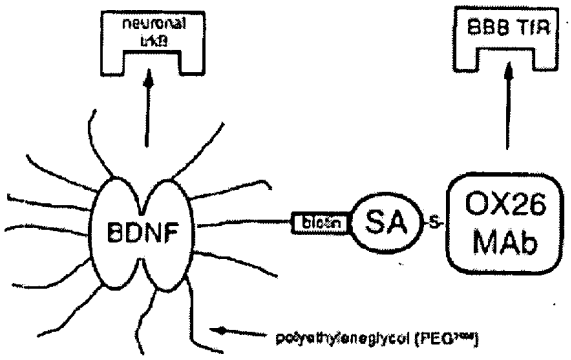
peptide/protein arts. One would have been also further motivated with reasonable expectation of success to modify the PEG moiety to extend BBB transport as taught by Wu et al given Wu's clear teaching that this is extendable to many other neuropeptides with only the need for optimization. Therefore, it would have been prima facia obvious to one of ordinary skill in the art at the time of the instantly claimed invention to substitute a PEGylate biphalin and conjugate the biphalin PEG to OX26/Strepavidin for improved pharmacokinetics and BBB transport.

Applicant's arguments filed 8/3/2007 have been fully considered but they are not persuasive. Applicant have argued:

The claims under consideration are directed to a hydrophilic polymer-peptide conjugate consistin.q essentially of a peptide that is either biphalin or [D-Pen2, D-Pen5] enkephalin (DPDPE) covalently linked to one or more polyethylene glycol or ethylene glycol-propylene glycol co-polymer chains having a molecular weight from about 2,000 to about 100,000 daltons, where the conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier. Additional optional features of the polymer can be found in claim 1. The conjugates of the claimed invention are absent a lipophilic moiety or any sort of transport vector, both of which were thought at the time of the invention to be critical to the transport of peptides such as DPDPE or biphalin across the BBB. In view of the above, it is submitted that the Examiner is improperly extending the teachings of the general PEGylation reference of Delgado to the instant claims, and failing to acknowledge the state of the art as a whole at the time of the invention, particularly with respect to neuropeptides such as those claimed, and their inability to cross the BBB. For instance, Wu actually teaches away from the Applicant's claims, since Wu teaches that in order for a neurotrophic factor such as BDNF to cross the blood brain barrier, it must not only be modified to possess optimized plasma pharmacokinetics (e.g., via covalent attachment to PEG), but must also be conjugated to a transport vector such as OX26 mAB. The conjugates of the Applicant's claims are clearly absent such a feature. To modify the teachings of Wu to arrive at the claimed invention, one would not only have to change the described neurotrophic factor to a small neuropeptide such as biphalin or DPDPE, but would further have to eliminate a feature of Wu stated to be critical for transport of BDNF across the BBB - i.e., the transport vector. Such a modification would, when viewed without the benefit of hindsight provided by the Applicant's

application, render the conjugate of Wu inoperable for transport across the BBB. The Examiner is reminded that: "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Thus, the combination of references relied upon by the Examiner fails to provide any motivation whatsoever to modify the teachings therein to arrive at a conjugate of the type embodied in the Applicant's claims.

These arguments are not found persuasive for two reasons. The first is that Claim 1 is still drafted in open language and can have more components that just a peptide and a PEG molecule(s):



The illustration (supra) from Wu et al construction of a PEGylated BDNF peptide is fully readable on a hydrophilic polymer-peptide conjugate consisting essentially of a peptide that biphalin (or BDNF from Wu et al) and the remaining biotin-SA-X26-MAb is readable on the consisting essentially of portion of the claim. Even absent the open language it still would be obvious to PEGylate a peptide for the plurality of reasons Delgado et al teaches as the art is replete with PEGylated peptides. Secondly, the Applicants have argued that Wu teaches away from the Applicant invention. This is not found persuasive either because the neuroacitve peptide of BDNF is pegylated and Applicants are claiming a composition that is pegylated and attempting to give patentability to the

property of the composition rather than the composition itself. If Wu et al had PEGylated another portion of the above composition, say the OX26 or MAb portion of the composition, then Applicants arguments may have been persuasive. However, the neuropeptide of BDNF is PEGylated and it logically follows that the properties of the PEGylated peptide described in the *wherein clause* would necessarily have to be present. Given that the PEG brings the properties BBB transport, upon substitution of biphalin for BDNF, those properties logically follow. Therefore, the rejection set forth above under 35 USC § 103 stands.

Conclusion

No claims are allowed.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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10/11/07
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